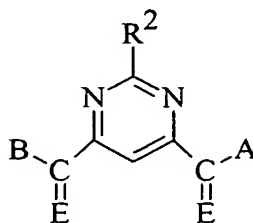


CLAIMS

What is claimed is:

1. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering an MMP inhibiting amount of a compound of Formula I



or a pharmaceutically acceptable salt thereof,
wherein:

R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

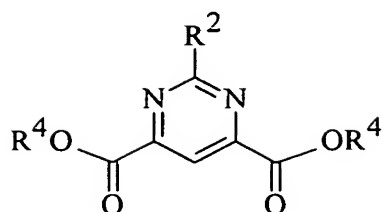
E is independently O or S;

A and B independently are OR⁴ or NR⁴R⁵;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

n is an integer from 0 to 6.

2. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering an MMP inhibiting amount of a compound of Formula II



II

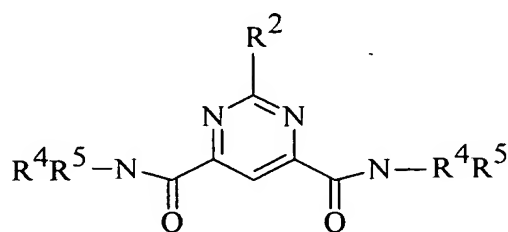
or a pharmaceutically acceptable salt thereof,

wherein R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃; and

each R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted.

3. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering an MMP inhibiting amount of a compound of Formula III



III

or a pharmaceutically acceptable salt thereof,

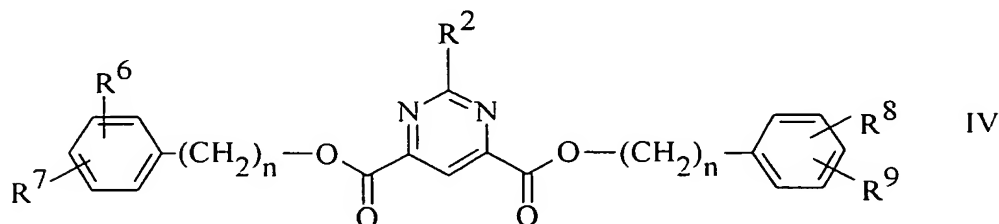
wherein R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon

atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted.

4. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering an MMP inhibiting amount of a compound of Formula IV

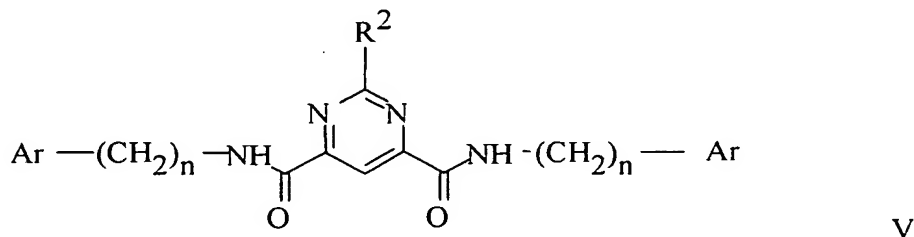


or a pharmaceutically acceptable salt thereof,

wherein n is 0 to 6;

R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃; each R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted; and R⁶, R⁷, R⁸, and R⁹ independently are hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, nitro, or NH₂.

5. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering an MMP inhibiting amount of a compound of Formula V



or a pharmaceutically acceptable salt thereof,

wherein n is 0 to 6;

R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆

alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

5 R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆

alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵

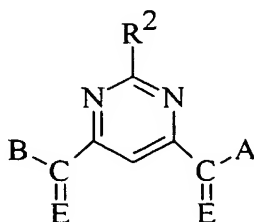
when taken together with the nitrogen to which they are attached complete
a 3- to 8-membered ring, containing carbon atoms and optionally
containing a heteroatom selected from O, S, or NH, and optionally
substituted or unsubstituted;

Each Ar independently is aryl or Het;

Aryl is phenyl or substituted phenyl;

Het is an unsubstituted or substituted heteroaryl group.

15 6. A compound having Formula I



or a pharmaceutically acceptable salt thereof,

wherein:

R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆

20 alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

E is independently O or S;

A and B independently are OR⁴ or NR⁴R⁵;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆

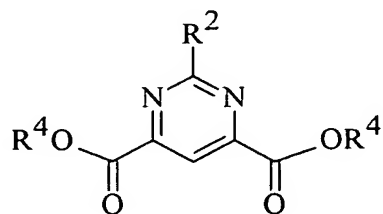
alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴

25 and R⁵ when taken together with the nitrogen to which they are

attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

n is an integer from 0 to 6.

- 5 7. A compound of Formula II



II

or a pharmaceutically acceptable salt thereof,

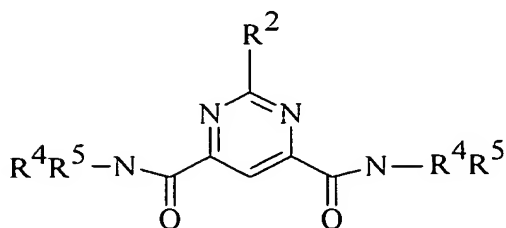
wherein R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃; and

10 each R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with a nitrogen to which they are both attached complete a 3- to 8-membered ring, containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

15 n is an integer from 0 to 6.

8. A compound of Formula III



III

or a pharmaceutically acceptable salt thereof,

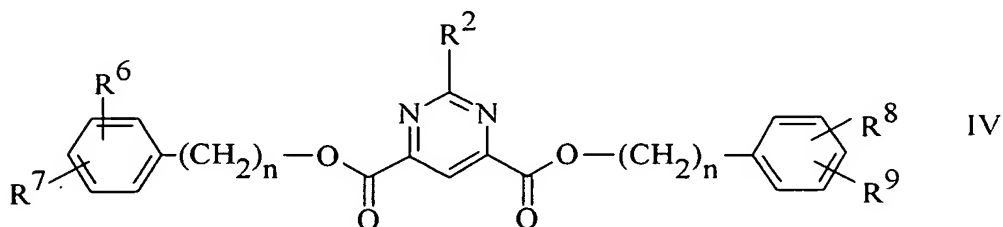
20 wherein R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

R^4 and R^5 independently are H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(CH_2)_n$ aryl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ heteroaryl, or R^4 and R^5 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

n is an integer from 0 to 6.

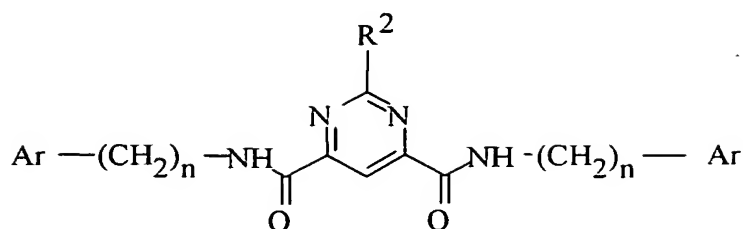
9. A compound of Formula IV



or a pharmaceutically acceptable salt thereof,
 wherein Each n independently is an integer of from 0 to 6;
 R^2 is hydrogen, halo, hydroxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, NO_2 , NR^4R^5 , CN, or CF_3 ; and R^6 , R^7 , R^8 , and R^9 independently are hydrogen, halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, nitro, or NH_2 ;

R^4 and R^5 independently are H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(CH_2)_n$ aryl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ heteroaryl, or R^4 and R^5 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted.

10. A compound of Formula V



V

or a pharmaceutically acceptable salt thereof,

wherein n is 0 to 6;

R² is hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆

5 alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆

alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵
when taken together with the nitrogen to which they are attached complete
a 3- to 8-membered ring containing carbon atoms and optionally
10 containing a heteroatom selected from O, S, or NH, and optionally
substituted or unsubstituted

Each Ar independently is aryl or Het;

Aryl is phenyl or substituted phenyl;

Het is an unsubstituted or substituted heteroaryl group.

15

11. A compound selected from:

Pyrimidine-4,6-dicarboxylic acid, (4-chloro-benzylamide), [(1,3-
benzodioxol-5-ylmethyl)-amide];

20

Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), [(1,3-
benzodioxol-5-ylmethyl)-amide];

Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (4-methoxy-
benzylamide);

Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (3-methoxy-
benzylamide);

25

Pyrimidine-4,6-dicarboxylic acid, (4-carbomethoxy-benzylamide),
(3-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide),
(3-pyridylmethylamide);

Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide).
(3-thiophenemethylamide);

5 Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl)
amide, [(1,3-benzodioxol-5-ylmethyl)-amide];

Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzooxadiazol-5-ylmethyl)
amide, [(1,3-benzodioxol-5-ylmethyl)-amide];

10 Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl)
amide, (4-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl)
amide, (3-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid bis-(1,3-benzodioxol-5-ylmethyl) ester;

Pyrimidine-4,6-dicarboxylic acid, bis-(4-chloro-benzylamide);

15 Pyrimidine-4,6-dicarboxylic acid, bis-[(1,3-benzodioxol-5-ylmethyl)-
amide];

Pyrimidine-4,6-dicarboxylic acid, bis-(4-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, bis-(3-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, bis-(4-carboxy-benzylamide); and

20 Pyrimidine-4,6-dicarboxylic acid, bis-(4-carbomethoxy-benzylamide).

12. A pharmaceutical composition, comprising an MMP-13 inhibiting amount
of a compound of Formula I, or a pharmaceutically acceptable salt thereof,
together with a pharmaceutically acceptable carrier, diluent, or excipient.

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13. The pharmaceutical composition according to Claim 12, comprising an
MMP-13 inhibiting amount of a compound of Formula II, or a
pharmaceutically acceptable salt thereof, together with a pharmaceutically
acceptable carrier, diluent, or excipient.

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14. The pharmaceutical composition according to Claim 12, comprising an
MMP-13 inhibiting amount of a compound of Formula III, or a

pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent, or excipient.

- 5 15. The pharmaceutical composition according to Claim 12, comprising an MMP-13 inhibiting amount of a compound of Formula IV, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent, or excipient.
- 10 16. The pharmaceutical composition according to Claim 12, comprising an MMP-13 inhibiting amount of a compound of Formula V, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent, or excipient.
- 15 17. The pharmaceutical composition according to Claim 12, comprising a compound selected from:
Pyrimidine-4,6-dicarboxylic acid, (4-chloro-benzylamide), [(1,3-benzodioxol-5-ylmethyl)-amide];
Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), [(1,3-benzodioxol-5-ylmethyl)-amide];
20 Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (4-methoxy-benzylamide);
Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (3-methoxy-benzylamide);
Pyrimidine-4,6-dicarboxylic acid, (4-carbomethoxy-benzylamide),
25 (3-methoxy-benzylamide);
Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (3-pyridylmethylamide);
Pyrimidine-4,6-dicarboxylic acid, (4-carboxy-benzylamide), (3-thiophenemethylamide);
30 Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl) amide, [(1,3-benzodioxol-5-ylmethyl)-amide];
Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzooxadiazol-5-ylmethyl) amide, [(1,3-benzodioxol-5-ylmethyl)-amide];

Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl)
amide, (4-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, (2,1,3-benzothiadiazol-5-ylmethyl)
amide, (3-methoxy-benzylamide);

5 Pyrimidine-4,6-dicarboxylic acid bis-(1,3-benzodioxol-5-ylmethyl) ester;

Pyrimidine-4,6-dicarboxylic acid, bis-(4-chloro-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, bis-[(1,3-benzodioxol-5-ylmethyl)-
amide];

Pyrimidine-4,6-dicarboxylic acid, bis-(4-methoxy-benzylamide);

10 Pyrimidine-4,6-dicarboxylic acid, bis-(3-methoxy-benzylamide);

Pyrimidine-4,6-dicarboxylic acid, bis-(4-carboxy-benzylamide); and

Pyrimidine-4,6-dicarboxylic acid, bis-(4-carbomethoxy-benzylamide), or a
pharmaceutically acceptable salt thereof, together with a pharmaceutically
acceptable carrier, diluent, or excipient.

15 18. A method for inhibiting an MMP-13 enzyme in an animal, comprising
administering to the animal an MMP-13 inhibiting amount of a compound
of Formula I, or a pharmaceutically acceptable salt thereof.

19. A method for treating a cancer, comprising administering to a patient
having cancer and in need of treatment an anticancer effective amount of a
20 compound of Formula I, or a pharmaceutically acceptable salt thereof.

20. A method for treating breast carcinoma, comprising administering to a
patient having cancer and in need of treatment an anticancer effective
amount of a compound of Formula I, or a pharmaceutically acceptable salt
25 thereof.

21. A method for treating heart failure, comprising administering to a patient
in need of treatment an effective amount of a compound of Formula I, or a
pharmaceutically acceptable salt thereof.

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22. A method for treating inflammation, comprising administering to a patient in need of treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
23. A method for treating osteoarthritis, comprising administering to a patient in need of treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
24. A method for treating rheumatoid arthritis, comprising administering to a patient in need of treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
25. A method of treating a disease or disorder selected from cancer, heart failure, inflammation, rheumatoid arthritis, and osteoarthritis, comprising administering to a patient in need of treatment an effective amount of a compound of Formula II, III, IV, or V, or a pharmaceutically acceptable salt thereof.

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